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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,715	04/19/2000	MAMORU OHASHI	2000-0486A	9675

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EXAMINER	
GOLLAMUDI, SHARMILA S	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,715	OHASHI ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,63-82 and 89-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20, 63-82, 89-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments and Arguments filed on September 9, 2004 is acknowledged. Claims 1-20, 63-82, 89-91 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 89-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term AS-3201 is not defined in the claims and renders the claim indefinite. The exmainer suggests defining the term in the independent claim of 89 akin to independent claim 1. Further, the claims recite the phrase "having an acidity more potent than that of AS-3201" which is vague and indefinite since the claims fail to define this term in numerical terms.

Response to Amendment

The Rule 132 declaration under 37 CFR 1.132 filed 9/9/04 is insufficient to overcome the rejection of claims based upon Negoro et al (5,258,382) in view of Muller et al (5,858,410) and Negoro et al (5,258,382) in view of Arbuthnot et al (6,458,811) as set forth in the last Office action for the following reason:

Firstly, it is unclear the purpose of the Rule 132 declaration, in terms of unexpected results. The examiner notes that the Rule 132 declaration of 9/9/04 does not specify the particle size, which is the main issue in the following rejections. The Rule 132 declaration is merely

demonstrating the solubility of AS-3201 in various solvents, which is not claimed. Therefore, the Rule 132 declaration is insufficient to overcome the following rejections.

The Declaration under 37 CFR 1.132 filed April 4, 2003 remains insufficient to overcome the rejection of claims based upon obviousness as set forth in the last Office action because:

Firstly, the claims are not commensurate in scope with the claims. The declaration provides for the lower limit of 1.5 microns, which is not recited in the claims and the amendment does not overcome this. As discussed previously, 1.001 is over 1 micron and therefore falls in the obvious range of the prior art. Again, the examiner suggests that the claims are changed to the lower range of 1.5 microns.

Secondly, the examiner points out that the unexpected results are very expected according to the Noyes-Whitney law that predicts that the larger the specific surface area of the drug substance, the faster the dissolution rate. The applicant's results indicate that 87-micron particles dissolve the slowest, then the 10-micron particles, with 1.5-micron particles having the fastest dissolution. Therefore, the applicant has not overcome the secondary reference since Muller et al clearly teaches this trend. Thirdly, the applicant is arguing against the Muller reference and yet has not provided unexpected results with the relevant art. Applicant's declaration only demonstrates Muller's teachings and does not compare Muller's upper limit of the nanometer range and applicant's lower limit of the micrometer range.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejections of claims 1-20 and 63-82 under 35 U.S.C. 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Muller et al (5,858,410) are maintained.

Negoro et al teach the instantly claimed aldose reductase inhibitor compound in a pharmaceutical composition for the treatment of diabetes (see abstract). The reference discloses the aldose reductase inhibitor in fine granules (1%) with a diluent (73%), a binder (3%), a lubricant (1%), and disintegrator (22%) (See example 29).

Negoro et al does not specify the particle size of the active or the dissolution rate.

Muller et al teach pharmaceutical compositions containing an active that is insoluble or sparingly soluble in water, an aqueous medium, or solvent. Muller discloses that the dissolution rate increases as the particles surface area increases in accordance with the Noyes-Whitney law. As a result of the increased dissolution rate, the bioavailability increases (col. 1, lines 44-50). Muller discloses a marked increase in saturation solubility and in turn dissolution with the reduction of particle diameter and increased surface area from microns to nanometers (col.5, lines 58-60 and col. 7, lines 7-10). The reference teaches a particle in the range of 10 to 1,000 nm, corresponding 0.01 to 1 micron, and 65% dissolution rate within ten minutes (col. 2, lines 40, col. 14, lines 49-55 and figures).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Negoro and Muller and reduce the particle size of the active instant range. One would be motivated to do so since Muller et al disclose that an

increased surface area through reduction of particle size allows for a faster rate of dissolution. Although Muller teaches the range of 0.01 to 1 micron and instant range is "in a range above 1 micron", it is deemed obvious to a skilled artisan to manipulate and tweak the prior art's particle range to obtain optimum results thorough routine experimentation. Further, one would expect similar results since Muller teaches a sparingly soluble or insoluble drug and the instant active agent is also sparingly soluble. Therefore, a skilled artisan would be motivated to decrease the particle size to that of Muller's particle range to provide for a faster dissolving composition with increased bioavailability in the body.

Response to Arguments

Applicant argues that the saturation solubility taught in Muller et al pertains to the nanometer range and not the micrometer range.

Applicant's arguments have been fully considered but they are not persuasive. Firstly, the mere argument that Muller is concerned with nanometer ranges instead of applicant's micrometer ranges is insufficient since the nomenclature "micro" versus "nano" is not enough to distinguish over the art since Muller teaches the upper limit of 1000nm, which when converted into micrometers is 1 micrometer. Therefore, depending on an artisan preference to call the particle size 1000 nanometers or 1 micrometer, the particle size remains the same. Thus, the obviousness rejection is based on the fact that Muller et al teach a range of 0.01 to 1 micron or 10nm to 1000nm and applicant merely recites "above 1 micron" which falls under an obvious scope and parameter of the prior art. For instance, 1.001 is above Muller's 1 micron, however it is still an obvious parameter to a skilled artisan thorough routine optimization.

With regard to applicant's argument that Muller teaches that a particle size above 5 microns is not suitable since it would block the veins. The examiner is not arguing the fact that Muller utilizes a range of 0.01 to 1 micron and does not teach applicant's entire range. The examiner is utilizing Muller to reject part of the broad range, i.e. "above 1 micron".

Applicant argues that Negoro et al do not teach the instant particle range and that Muller et al do not demonstrate that a *solid compound* having an increased surface area exhibits a faster dissolution out of the composition.

Applicant's arguments have been fully considered but they are not persuasive. It is firstly pointed out that the broad terminology "solid dosage forms" encompasses Muller's nanosuspensions since suspensions are solid particles suspended in an immiscible liquid. Thus, Muller does in fact teach solid particles. Moreover, applicant argues that the tablets dissolve quickly and this is the "inventive discovery" as shown in examples 1 and 2 of the instant specification. However, the examiner points out that the claims do not recite a tablet form and the applicant is relying on a feature that is not recited in the claims. Moreover, the examples utilize a specific tablet composition which is not recited in the claims. Therefore, the claims are not commensurate in scope with the examples in the instant specification the show the unexpected results. Again the examiner points out that the Noyes-Whitney law does not only apply a certain type of pharmaceutical composition, rather it is a theory that can be applied to a variety of pharmaceutical compositions.

Rejections of claims 1-20 and 63-82 under 35 U.S.C. 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Arbuthnot et al (6,458,811) is <u>maintained</u>.

Negoro et al teach the instantly claimed aldose reductase inhibitor compound in a pharmaceutical composition for the treatment of diabetes (see abstract). The reference discloses the aldose reductase inhibitor in fine granules (1%) with a diluent (73%), a binder (3%), a lubricant (1%), and disintegrator (22%) (See example 29).

Negoro et al does not specify the particle size of the active or the dissolution rate.

Arbuthnot et al teach a benzothiophene compound in particulate form with a mean particle size between 5 and about 20 microns. See column 2, lines 66-67. Arbuthnot states that it has been found that tweaking the particle size within a specified range, the pharmaceutical composition may be prepared to exhibit a consistent vitro dissolution profile and in vivo bioavailability. Further, the reference states that by controlling the particle size to a narrow range, it has also results in improved manufacturing capabilities. See column 3, lines 15-32. It is noted by Arbuthnot that a compromise between the particles size and manufacturing exists, however the method for determining the particle size is known in the art. See column 22, lines 16-56. Arbuthnot states that compounds with poor solubility can have their bioavailability enhanced by increasing the surface area of the particles. Further, Arbuthnot states that the aqueous solubility of a drug potentially impacts the dissolution rate of the solid dosage form since the dosage form and the active are exposed to the gastrointestinal tract. Thus, the two related physical properties of drugs, the surface area and particle size, can alter the dissolution rate of the dosage form. The impact of surface area, which is a function of particle size is illustrated by the Noyes-Whitney equation. See column 24, lines 25-55.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Negoro and Arbuthnot et al and reduce the particle size of

the active to the instant range. One would be motivated to do so since Arbuthnot discloses that an increased surface area through reduction of particle size allows for a faster rate of dissolution of the active and the solid dosage form. Further, Arbuthnot et al teach that increasing the surface area thorough the reduction of particle size, as taught by the Noyes-Whitney law, increases the bioavailability of sparingly soluble drugs. Thus, one would be motivated to encompass the teachings of Arbuthnot since the instant active agent is also sparingly soluble.

Therefore, a skilled artisan would be motivated to decrease the particle size to that of Muller's particle range to provide for a faster dissolving composition with increased bioavailability in the body.

Note that the dependent claims that recite a range of less than 5 microns and 1 micron to 5 microns, are deemed to be obvious parameters in the art done thorough routine experimentation to obtain the best results. One would be motivated to do so since Arbuthnot teaches that the method of determining the best mean particle size for a drug is readily known to one of ordinarily skill in the art. Further, Arbuthnot provides the guidance in experimenting to find the optimal particle size.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicants argue that Arbuthnot's raloxifene and instant AS-3201 are not the same compounds. Applicant argues that Arbuthnot teaches milling is not practical or desirable. Lastly, applicant argues that the Noyes-Whitney law cannot apply to every compound.

Firstly, the examiner notes that the two drugs are not the same, otherwise Arbuthnot would anticipate the instant invention. The examiner utilizes the secondary reference to teach the

Noyes-Whitney law, which Arbuthnot teaches in a general manner in reference to solid dosage forms. See column 24, lines 25-55.

With regard to the argument that Arbuthnot does not prefer the milling process, the examiner points out that the claims are product claims and not method of making claims. Thus, the method in which the particle size is yielded has not bearing on the product itself.

With regard to the assertion that the Noyes-Whitney law does not apply to every compound, the examiner does not assert that this law applies to every compound known. The examiner merely notes that this is a general theory that is a starting point to experiment. If this theory does not apply to the instant compound, then the applicant must show this in a Rule 132 declaration since the USPTO is not capable of performing such tests. The examiner notes that the applicant has still not compared a nanometer range, i.e. the range outside the claimed lower limit, and the instant micrometer range of the instant drug to overcome the rejections based on the Noyes-Whitney law.

For the above reasons, the rejections are maintained.

New claims 89-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Negoro et al (5,258,382) in view of Muller et al (5,858,410) or Arbuthnot et al (6,458,811) in further view of Schneider et al (5,356,636).

As set forth above, Negoro et al teach the instant active in a solid dosage form. Muller et al and Arbuthnot et al teach the reduction of particle size to increase dissolution. Muller et al teach the use of stabilizers to cover the surface of the particles to prevent aggregation (col. 7).

The references do not teach the instant acids in the composition.

Schneider et al teach the use of stabilizers or antioxidants when the active agent is sensitive to oxidation. Stabilizers such as the instant acids of claims 61 and 62 are taught on column 4, line 68.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add the instant acids in the composition of Negoro et al. One would be motivated to do so since Schneider et al teach these acids as stabilizers for the active agents. Thus, it is considered obvious to a skilled artisan to pursue the stability of an active against oxidation.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that one of ordinary skill cannot determine if AS-3201 is susceptible to oxidation and needs stabilization.

It is the examiner's position that determining if a compound is stable or unstable is a routine skill in the art. If applicant asserts that the instant acids provide unexpected stability than that taught in the prior art, the examiner suggests submitting a Rule 132 declaration demonstrating this.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20, 61-82, and new claims 89-91 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,297,244 in view of Arbuthnot et al (6,458,811).

US patent claims a pharmaceutical composition containing AS-3201 and "at least one acidic substance having an acidity more potent than that of said active ingredient." Claims 4-6 recite an acidic Markush group of citric acid, tartaric acid, maleic acid, and phosphoric acid.

Instant application claims a solid dosage form containing "AS-3201" (Note the chemical name in claim 1) with a mean particle size in a range of above 1 micron to less than about 20 microns. Claim 61 claims a stabilizer of "at least one acidic substance having an acidity more potent than that of AS-3201". Claim 62 claims an acidic Markush group of citric acid, tartaric acid, maleic acid, and phosphoric acid.

US patent does not claim the instant particle size.

Arbuthnot et al teach a benzothiophene compound in particulate form with a mean particle size between 5 and about 20 microns. See column 2, lines 66-67. Arbuthnot states that it has been found that tweaking the particle size within a specified range, the pharmaceutical composition may be prepared to exhibit a consistent vitro dissolution profile and in vivo bioavailability. Further, the reference states that by controlling the particle size to a narrow range, it has also results in improved manufacturing capabilities. See column 3, lines 15-32. It is noted by Arbuthnot that a compromise between the particles size and manufacturing exists, however the method for determining the particle size is known in the art. See column 22, lines

16-56. Arbuthnot states that compounds with poor solubility can have their bioavailability enhanced by increasing the surface area of the particles. Further, Arbuthnot states that the aqueous solubility of a drug potentially impacts the dissolution rate of the solid dosage form since the dosage form and the active are exposed to the gastrointestinal tract. Thus, the two related physical properties of drugs, the surface area and particle size, can alter the dissolution rate of the dosage form. The impact of surface area, which is a function of particle size is illustrated by the Noyes-Whitney equation. See column 24, lines 25-55.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of US patent and Arbuthnot et al and utilize the instant application particle range. One would be motivated to do so since Arbuthnot discloses that an increased surface area through reduction of particle size allows for a faster rate of dissolution of the active. Further, Arbuthnot et al teach that increasing the surface area thorough the reduction of particle size, as taught by the Noyes-Whitney law, increases the bioavailability of sparingly soluble drugs. Thus, one would be motivated to encompass the teachings of Arbuthnot since the instant active agent is also sparingly soluble. Therefore, a skilled artisan would be motivated to decrease the particle size to that of Muller's particle range to provide for a faster dissolving composition with increased bioavailability in the body.

Conclusion

All claims remain rejected at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616

SSG

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